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It was further discovered by [Chang] Cheng, D. *et al.* (1999) J. Biol. Chem. 274.22805-22812 that an enzyme called S1p, is capable of cleaving sterol-regulatory element-binding proteins (SREBPs), which function to control lipid biosynthesis and uptake in animal cells. Upon cleavage, SREBPs are released from cell membranes for translocation to the nucleus, where they activate transcription of genes involved in the biosynthesis and uptake of cholesterol and fatty acids. S1p and the present enzyme or the same. Therefore, for diseases involving overexpression of these genes as well as any other disease involving SKI-1 activity, it is contemplated that any inhibitor of SKI-1 would be useful in their treatment.

Genetic and biochemical evidence indicates that SKI-1/S1p is the protease that cleaves sterol-regulatory element-binding proteins (SREBPs) which functions to control lipid biosynthesis and uptake in animal cells { Sakai, J. et al. (1998) Molecular Cell 2, 505-514; Cheng, D. et al. (1999) J. Biol. Chem. 274, 22805-22812; Toure, A. et al. (1999) In: Peptides for the Now Millennium: Proceedings of the 16th American Peptide symposium}. SKI-1 and SREBPs play critical roles in the feedback pathways by which cholesterol suppresses transcription of genes encoding HMG CoA reductase and other enzymes of cholesterol biosynthesis as well as the low density lipoprotein (LDL) receptor. A SKI-1 inhibitor would be of use under clinical conditions in which there is not sufficient down regulation of SREBP dependent transcription by sterols. For example, in the Nieman-Pick group of diseases a high sphingomylin content of cells leads to an increase in proteolysis of SREBP-2 and a subsequent increase in cholesterol biosyntheses { Scheek, S. et al. (1997) Proc. Natl. Acad. Sci. USA 94, 11179-11183; Spence, M.W., and Callahan, J.W. (1989) Spingomyelin-cholesterol lipidoses: The Nieman-Pick Group of Diseases. *In The Metabolic Basis of Inherited Disease*) Scriver, C.R., Beaudet, A.L., Sly, W.S., and Valle, D., editors), McGraw-Hill Publ. Co., 6th edition, chapter 66, [1655-1675] 1655-1676; [Svirirodov] Sviridov, D. (1999) Histology & Histopathology 14 (1): 305-319 }. Perhaps of greater significance, nuclear SREBP-1c protein levels were significantly elevated in mouse models for non-insulin dependent diabetes, *ob/ob* and aP2 SREBP-1c mice, which was associated with elevated mRNA levels for known SREBP target genes involved in the biosynthesis of fatty acids (Schimomura, I. *et al.* J. Biol. Chem. 1999; 274:30028-30032).

Results of immunocytochemistry performed in mouse lacrimal glands provides evidence for the presence of SKI-1 and APP in the same cells types, including intralobular duct epithelial cells and some acinar cells (Fig. 26). The finding of SKI-1 in the lacrimal gland suggests the possibility of developing a diagnostic assay analyzing tears; perhaps based on two-dimensional polyacrylamide gel electrophoresis for disease diagnosis { Moley, M.P. et al. (1997) Electrophoresis 18, 2811-2815; Glasson, M.J. et al. (1998) Electrophoresis 19, 852-855; Grus, F.H., and Augustin, A.J. (1999) Electrophoresis 20, 875-880; Iskeleli, G. et al. (1999) [Electrophoresis 20, 875-880 }.] CLAO Journal, 25:101-104;

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